

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: Paul CLOOS *et al.*

Application No.: To be assigned

Group Art Unit: To be assigned

Filed: February 15, 2002

Examiner: To be assigned

For: DETECTION OF ISOMERISED EPITOPES
IN AUTOIMMUNE DISEASES

Attorney Docket No.: 8969-032

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Prior to examination of the application filed herewith, please consider and enter the following amendments into the file of the above-captioned application.

IN THE SPECIFICATION:

Immediately after the title on page 1, please insert the following: --This is a continuation of International Application No. PCT/EP00/07973, which has an international filing date of August 16, 2000 and which claims priority to GB 9919452.4, filed August 17, 1999.--

IN THE CLAIMS:

Please cancel claims 1-19 without prejudice and add the following new claims:

-- 20. (New) A method of assay comprising subjecting a sample to a quantitative or qualitative determination of the presence in a sample of (a) an auto-reactive immune system component specifically recognising an epitope containing an isomerised peptide linkage and/or an optically inverted amino acid, and/or (b) an auto-antigen or a fragment thereof

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containing said epitope and/or (c) a non-self antigen or fragment thereof which contains said epitope and is capable of inducing an autoimmune response.

21. (New) The method of claim 20, wherein said immune system component is a cellular immune system component.

22. (New) The method of claim 21, wherein said immune system component is a T-lymphocyte.

23. (New) The method of claim 20, wherein said immune system component is a humoral immune system component.

24. (New) The method of claim 23, wherein said epitope comprises an amino acid sequence derived from IgG containing an isomerised peptide linkage or an optically inverted amino acid.

25. (New) The method of claim 23, wherein said immune system component is an auto-antibody directed against an epitope comprising the amino acid *Asx contained in any one of the sequences:

Trp-Leu-*Asx-Gly-Lys -Glu-Tyr;

Trp-Glu-Ser-*Asx-Gly;

His-Phe-Phe-Lys-*Asx-Ile-Val-Thr-Pro;

Pro-Ser-*Asx-Glu-Gly-Lys-Gly-Arg;

Ala-Leu-Gly- Ile-Gly-Thr-*Asx-Ser-Val-Ile;

Trp-Ser-Phe-Gly-Ser-Glu-*Asx-Gly-Ser-Gly-*Asx-Ser-Glu-Asn;

Ala-Gly-Trp-Leu-*Asx-Gly-Ser-Val-Arg; or

Gly-Arg-Val-Arg-Val-*Asx-Ser-Ala-Tyr

wherein Asx* is α D Asp or Asn, or is β L or β D, Asp formed by isomerisation/optical inversion of Asp, or Asn residues in the original sequence.

26. (New) The method of claim 23, wherein said immune system component is an auto-antibody directed against an epitope comprising the amino acid *Asx contained either of the sequences:

Met-Glu-Val-Gly-Trp-Tyr-Arg-Pro-Pro-Phe-Ser-Arg-Val-Val-His-Leu-Tyr-Arg-
*Asx-Gly-Lys; or

Val-Val-His-Phe-Phe-Lys-*Asx-Ile-Val-Thr-Pro

wherein *Asx is α D Asp or Asn, or is β D, or β L Asp formed by isomerisation/optical inversion of Asp or Asn residues in the original sequence.

27. (New) The method of claim 23, wherein said immune system component is an auto-antibody directed against an epitope comprising the amino acid *Glx contained in any one of the sequences:

Pro-Ser-*Glx-Gly-Lys-GlyArg;

Pro-Ser-Trp-Gly-Ala-*Glx-Gly-Arg; or

Asp-Ala- *Glx-Gly-Thr-Leu-Ser-Lys

wherein *Glx is α D Glu or Gln, or is γ L or γ D Glu formed by isomerisation/optical inversion of Glu or Gln residues in the original sequence.

28. (New) The method of claim 20, wherein detection of said immune system component or auto-antigen is indicative of an auto-immune disease.

29. (New) The method of claim 28, wherein said disease is rheumatoid arthritis, multiple sclerosis, insulin dependent diabetes mellitus, myasthenia gravis, celiac disease, Chagas' disease, psoriasis, or Crohn's disease.

30. (New) A method for the detection of an auto-antigen or fragment thereof comprising detecting the reactivity of said auto-antigen or fragment with an immunological

binding partner specific for the presence in said auto-antigen of an isomerised peptide linkage or an optically inverted amino acid.

31. (New) The method of claim 30, wherein said immunological binding partner is specific for an epitope as defined in claim 25.

32. (New) The method of claim 20 or 30, wherein information as to the amount of said immune system component or auto-antigen or non-self antigen or antigen fragment detected is obtained.

33. (New) A method for locating an epitope or epitopes in an auto-antigen comprising using L-iso-aspartyl (D-aspartyl) methyl-transferase (IAMT) and a source of labelled methyl groups to introduce said labelled methyl groups at one or more isomerised peptide linkage and/or optically inverted amino acids in said auto-antigen, and determining at least one location in said auto-antigen at which said labelled methyl groups are thus introduced, establishing the amino acid sequence of said auto-antigen in a region encompassing said location and testing a peptide of said amino acid sequence incorporating at said location said isomerised or optically inverted amino acid for immunoreactivity with an auto-reactive immune system component.

34. (New) The method of claim 33, wherein the auto-antibodies are associated with an autoimmune disease.

35. (New) The method of claim 33, wherein the autoimmune disease is rheumatoid arthritis, multiple sclerosis, insulin dependent diabetes mellitus, myasthenia gravis, celiac disease, Chagas' disease, psoriasis, or Crohn's disease.

36. (New) A peptide containing an epitope recognised by an auto-reactive immune system component, which epitope contains an isomerised peptide linkage and/or an optically inverted amino acid.

37. (New) The peptide of claim 36, which comprises an epitope as defined in Claim 6.

38. (New) The peptide of claim 37, comprising the altered amino acid residue *Asx, or *Glx and at least three flanking amino acid residues in the N-terminal and/or C-terminal direction, where *Glx is α D Glu or Gln, or is γ L or γ D Glu formed by isomerisation/optical inversion of Glu or Gln residues in the original sequence and where *Asx is α D Asp or Asn, or is β L or β D Asp formed by isomerisation/optical inversion of Asn or Asp residues in the original sequence. --

REMARKS

The specification has been amended to reflect the fact that this application is a continuation under 35 U.S.C. § 111(a) of International Application No. PCT/EP00/07973, which was filed August 16, 2000 and which claims priority to GB 9919452.4, filed August 17, 1999. Claims 20-38 are pending in this application.

No fee is believed due for the entry of this paper. However, if any fees are due for its entry or to prevent abandonment of this application, please charge such fees to Pennie & Edmonds Deposit Account No. 16-1150.

Respectfully submitted,

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